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Meiosis: When Even Two Is a Crowd

Dispatch

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Recent studies in *Caenorhabditis elegans* show that crossover interference, which usually limits the number of exchanges per meiotic bivalent to just 'one', requires the continuity of both homologs. One 'function' of crossover interference may be the prevention of crossover events that might not effectively hold homologs together.

Mendelian inheritance works because homologous chromosomes segregate from their partner at the first meiotic division. The ability of homolog pairs to segregate properly is facilitated by exchanges — or crossovers, if you went to a private school — which serve to physically inter-lock the homologous chromosomes until they separate properly at meiosis I. The ability of crossover events to connect homologs depends on the presence of sister chromatid cohesion distal to the site of exchange. As shown in Figure 1A, as long as that cohesion stays in place, the homologs stay connected [1]. As shown in Figure 1B, however, crossovers that occur too close to the ends of a bivalent will provide only minimal sister chromatid cohesion distal to the exchange, and if that cohesion lapses for whatever reason, segregation often fails [2,3]. Perhaps as an evolutionary adaptation to these constraints, in most organisms the position of an exchange along each arm is tightly controlled.

Several mechanisms underlie this precise control of crossover distribution. First, in many organisms there are *cis*-acting functions, such as the centromere and telomere effects, that serve to reduce exchange along the arms in a polar fashion (reviewed in [4]). There are also a number of *cis*-acting sites within the recombining regions of the euchromatin that serve to control the level of exchange in their vicinity [5,6]. But perhaps the most mysterious determinant of exchange position is a process known as crossover (or chiasma) interference. As described in an elegant study published recently in *Current Biology* by Hillers and Villeneuve [7], interference can act over quite large distances along the length of meiotic chromosomes to limit the number of exchanges that do occur to just 'one', and thus to reduce the probability of two or more exchange events. In most organisms this inhibition of additional crossover events diminishes in strength as one moves farther away from the initial crossover event.

Several lines of evidence suggest that crossover interference may require the transmission of either an inhibitory signal, or a reduction in the capacity to initiate exchange, along some large component of the chromosomes (such as a component of the synaptonemal complex). Presumably, the creation or relief of 'stress' at one site by the first exchange alters the conformation of that structure for long distances along the bivalent, and in doing so reduces the probability of a second exchange (reviewed in [8]). Indeed, Sym and Roeder [9] showed that mutants in a component of the synaptonemal complex appear to greatly reduce the level of crossover interference in yeast. The suggestion that some component of the synaptonemal complex may play a role in mediating crossover interference is at least consistent with studies demonstrating a positive correlation between the length of the synaptonemal complex and the number of crossovers in grasshoppers, mice and humans [10,11].

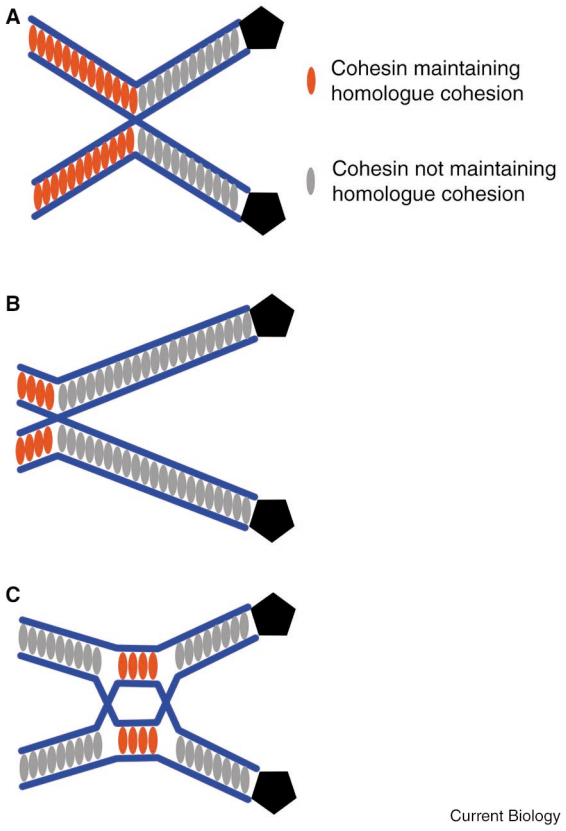

Figure 1. Crossovers (or chiasmata) serve to physically interlock homologous chromosomes by virtue of sister chromatid cohesion on both sides of the exchange.
(A) A normal bivalent. Note that because the sister chromatids in the vicinity of the centromere do not separate until meiosis II, the two homologs that comprise this bivalent will remain connected to each other until the sister chromatid cohesion distal to the exchange is removed at anaphase I. (B) A bivalent held together only by a very distal exchange. Such bivalents often fail to segregate properly [2,3], presumably because the relatively small amount of cohesion distal to the exchange lapses prematurely. (C) A bivalent with a 'two-strand' double crossover event. Note that, like the example presented in (B), the two homologs that make-up this bivalent are connected only by a very short region of sister chromatid cohesion. Lapse of that cohesion might easily cause precocious separation of the two homologs.

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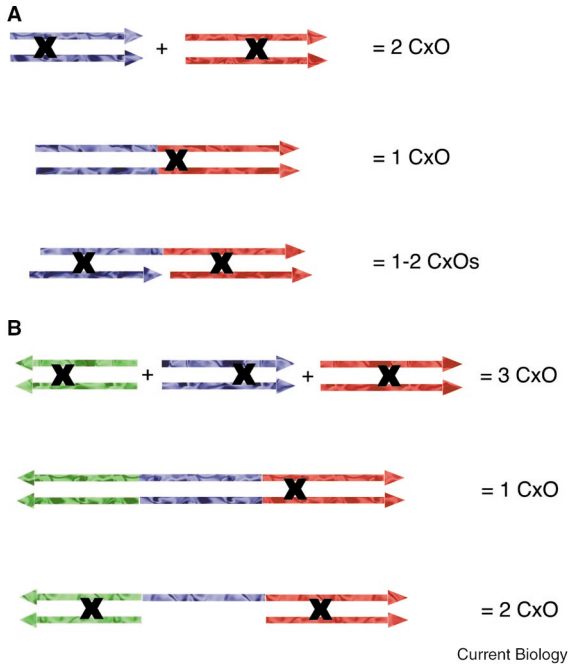

Figure 2. Summary of the experiments performed by Hillers and Villeneuve [7].

(A) Two pairs of homologs (top panel), each of which normally undergoes one crossover per meiosis, are fused to created a double fusion chromosome (middle panel). Despite a doubling of its length, the homozygous fusion chromosome still undergoes but one crossover per meiosis. When a heterozygote for the fusion chromosome and two normal homologs is tested (bottom panel), the two halves of the fusion chromosome now recombine with their homologs in more than half of the meioses. (B) Three pairs of homologs, each of which normally undergoes one crossover per meiosis (top panel), are fused to create a triple fusion chromosome (middle panel). Again, this fusion chromosome still undergoes but one crossover per meiosis. When a heterozygote for the fusion chromosome and two normal homologs is tested (bottom panel) the two ends of the fusion chromosome now recombine with their homologs in the vast majority of the meioses.

A stronger demonstration that interference is created by a spreading (or polar) process that can act over large distances on a given bivalent, and that it requires the continuity of some chromosomal or synaptonemal complex component, is provided by recent studies of crossover control in the *Caenorhabditis elegans*. This nematode may well be the ideal organism for studying interference, because each of the six chromosomes has a map length of 50 cM — so the vast majority of bivalents experience only one crossover per meiosis — and nonexchange bivalents are rare [7,12–14]. In other words, *C. elegans* appears to be especially proficient at inhibiting multiple crossovers.

Hillers and Villeneuve [7] have shown that this high level of interference is preserved even when two or three sets of homologs are fused together to create much larger chromosomes (Figure 2). Naively, one might have expected such double or triple fusion chromosomes to have approximately two or three crossovers, respectively, per bivalent. The finding that the fusion chromosomes are still limited to one exchange per bivalent shows that interference is powerful enough to act over intervals spanning two or three chromosome lengths — as much as half the genome — to maintain the number of crossovers at approximately one per bivalent. Thus, exchange levels are not controlled solely by discrete regional domains, but rather at the level of the entire chromosome, regardless of its length. Even this very powerful example of interference, however, can be attenuated at some length; some double crossovers do occur in triple fusion homozygotes, with a tendency to be widely spaced.

Hillers and Villeneuve [7] further demonstrated that the propagation of interference along the bivalent requires the physical continuity of both homologs . As shown in Figure 2, heterozygotes for either a double length fusion chromosome and two normal homologs, or a triple fusion and two homologs displayed substantially higher levels of exchange — including double crossovers — and thus reduced levels of interference. In the case where the double length fusion chromosome pairs with two normal homologs, interference was substantially reduced, as evidenced by the fact that both normal homologs experienced a crossover with the fusion chromosome in about half of meioses. Moreover, in the instance of the triple fusion and two normal homologs, a case in which there is a large structural discontinuity in the middle, each of the two paired regions underwent an average of one exchange with the homologous fusion chromosome. These observations suggest that components of both homologs — or both sides of the synaptonemal complex — may serve to propagate some type of signal that generates interference, in a manner that requires their continuity.

The mechanism by which interference acts remains a mystery. One clue may come from the observation by Meneely *et al.* [14] that, in the few cases where double crossovers were observed in a normal bivalent, one occurred in a terminal interval referred to as the pairing region. This region has the capacity to stabilize pairing even in the absence of synapsis [15], and thus might define a region where differences in some component of the chromosomes are unable to initiate interference. If so, then understanding the method by which pairing regions function might also provide useful insights into the mechanism of interference.

All of this nonetheless begs the more serious question, namely why is there interference? It clearly is not necessary; organisms such as the fungus *Aspergillus* and fission yeast *Schizosaccharomyces pombe* lack both interference and the synaptonemal complex. But they nevertheless manage to do a crossover-based meiosis quite nicely; indeed, in both organisms the number of exchanges per bivalent is quite high! So it can not be the case that interference is an obligate component of the process of crossingover. In *C. elegans*, such high levels of interference may be required by the unusual manner in which this normally holocentric organism completes meiosis [16]. Despite the apparent presence of a diffuse kinetochore, at meiosis I [17], whichever pair of ends is most distant from the crossover appear to lead the way to the poles at anaphase I [18,19]. The pair of ends closest to the

crossover must then release sister chromatid cohesion between the crossover and the ends in order to allow the bivalent to segregate at anaphase I [16]. Thus, the presence of two crossovers in *C. elegans* might actually impede the segregational process, either by impairing kinetochore orientation towards the poles by reducing the distance from either end to a crossover, or by requiring the release of sister chromatid cohesion at both ends (or over rather long portions of the bivalent [16]).

But for most organisms, the position of the centromere is tightly defined, and the prohibition of crossovers in the peri-centric heterochromatin, allows the kinetochores substantial room to 'move'. In such organisms, we propose that the function of interference lies not in the mechanism that generates crossingover, but rather in the function of exchange itself. As noted above, chiasmata function to bind homologs together by virtue of the sister chromatid cohesion lying distal to the crossover and the fact that sister centromeres maintain together throughout the first meiotic division.

But the simple presence of any amount of cohesion distal to the crossover is not enough — the amount of sister chromatid cohesion distal to the site of crossingover is also critical. Bivalents in which a single crossover occurs too distally have too little distal sister chromatid cohesion and thus are not stably conjoined. As shown in Figure 1C, this is also the case for those closely linked double crossover bivalents in which both crossovers involve the same two chromatids — so-called 'two-strand doubles'. Such two-strand double exchange bivalents will be held together only by cohesion of sisters in the short interval between the two exchanges. This may well not be enough to ensure homolog—homolog conjunction. Although this problem would not be shared by those types of double exchange that involve more than two chromatids — three-strand and four-strand doubles — it may simply have proved easier to space doubles far apart than to try and restrict double exchange events in a fashion that precludes the occurrence of two strand doubles.

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